DOCKET NO: 294685US0PCT

IN THE UNITED STATES PATENT & TRADEMARK OFFICE

IN RE APPLICATION OF		:
ROB HOOFT VAN HUIJSDUIJNEN, ET AL.		: EXAMINER: WEBB
SERIAL NO: 10/590,808		:
FILED:	JANUARY 12, 2007	: ART UNIT 1612
FOR:	USE OF METHYLENE AMIDE DERIVATIVES IN CARDIOVASCULAR DISORDERS	:

REPLY BRIEF

COMMISSIONER FOR PATENTS
ALEXANDRIA, VIRGINIA 22313

SIR:

This Brief is submitted in response to the Examiner's Answer (hereinafter "Answer") issued on November 30, 2009.

The invention is to a method of treatment of coronary obstruction or peripheral vasoconstriction using compounds of Formula (I). This treatment is independent of whether or not the patient has diabetes.

The Answer at page 6 restated the conclusion of obviousness as follows:

> It would have been obvious to a person having ordinary skill in the art at the time of applicant's invention to administer the compounds of Liu for the treatment of coronary obstruction and peripheral vasoconstriction, since they are problems associated with diabetes, as taught by Sowers et al. and Parissis et al. The artisan would reasonably expect success in treating coronary obstruction or peripheral vasoconstriction in a patient by administering the compounds of Liu to diabetic patients since hypertension and diabetes frequently coexist and each pathophysiological disease entity serves to exacerbate the other, as taught by Sowers et al. Thus, in treating diabetes the artisan would reasonably expect a positive effect on hypertension and cardiovascular disease.

Thus, in the Examiner's construct of the prior art as diabetic patients may develop coronary obstruction or peripheral vasoconstriction, it would have been obvious to treat diabetes with Liu's compounds, and it would have been reasonably expected that coronary obstruction or peripheral vasoconstriction (the subject matter defined in the claims) would also be successfully treated. See also page 11 of the Answer. Further in the paragraph bridging pages 6-7 of the Answer, under the Examiner's construction by treating one disease (diabetes) the other would be prevented or lessened to some degree.

In response, Appellants respectfully disagree and again submit that the Examiner's findings and conclusions based on those findings are clearly erroneous. While it is probable that in some patients, the reduction of diabetes from the prior art construct may reduce the risks associated with cardiovascular diseases (CVDs) such as coronary obstruction and/or peripheral vasoconstriction, presuming that the patient has not developed such CVDs, the treatment of diabetes cannot be simply concluded that it would be reasonably expected to treat the underlying physiological problems of CVDs, which are a vastly different set of diseases having at best inconclusive evidence that diabetes treatment effects CVDs as well.

Indeed, there are a number of diseases associated with diabetes whether caused by diabetes or vice versa. See, for example, Sowers at page 1057 discussing relationships between diabetic cardiomyopathy and microaluminuria, amongst others. As is notoriously well-known, diabetes is caused by a problem with or deficient response to insulin. Insulin is produced by the pancreas and can have many different etiologies, such as genetic mutations, obesity and others. While diabetes may lead in some patients to CVDs such as coronary obstruction and/or peripheral vasoconstriction (the subject matter defined in the claims), it is also the case that diabetes has no relationship to CVDs (see, e.g., Sowers in the Abstract, at least 25% of patients do not have a correlation between CVD, diabetes and hypertension).

CVD is simply more likely to occur in a diabetic patient relative to a healthy subject, that is the correlation made by Sowers in the Abstract. What the causative effect or link between diabetes and CVDs has not been established by the art cited in the rejection.

It is notoriously well-known in the art that CVDs can arise from any number of very different factors, such as age, gender, genetics, tobacco, cholesterol, physical inactivity, obesity, stress, and alcohol. In addition, as discussed by Parissis (cited in the rejection) numerous inflammatory mediators may also be involved or give rise to an increased risk for developing CVDs such as coronary obstruction or peripheral vasoconstriction that has nothing to do with diabetes (see also the present specification at page 3).

Further, as explained by the Court of Appeals for the Federal Circuit:

> . . . an invention is not obvious to try where vague prior art does not guide an inventor toward a particular solution. A finding of obviousness would not obtain where "what was 'obvious to try' was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or

> how to achieve it." This expresses the same idea as the KSR requirement that the identified solutions be "predictable."
>
> Bayer Schering Pharma AG v. Barr Laboratories, Inc. *2009* U.S. App. LEXIS 17372, 91 U.S.P.Q.2D (BNA) 1569 (Fed. Cir. 2009) (internal citations omitted)

The present specification explains that the invention resides in treating coronary obstruction and peripheral vasoconstriction, typically associated with heart failure using the compounds defined in the claims (see page 1, line 5-9). That the cited references teaches very different diseases, with only general disclosure as to what may be increased risk factors for CVDs associated with diabetes, there is simply nothing in the art that suggests the problem underlying the present invention. The disclosures that are relied upon in the rejection are only "general guidance" (*Id.*) and simply not the "finite disclosure" and guidance to "a particular solution" that the law requires. (*Id.*)

Under the Examiner's construct of the prior art (see page 6, 7 and 11 of the Answer), it would have been reasonably expected that diseases or conditions such as those defined in the claims of significantly different biological tissue with vastly different etiologies could be treated simply because the compounds defined in the claims were known (or obvious from the rejection) to treat diabetes and diabetic patients have an increased risk of CVDs relative to a healthy patient. This conclusion simply does not take into account the true nature of the complexities of biological systems and clinical treatments. Notwithstanding the increased risk that diabetic patients may have to develop CVDs (which is what Sowers describes); the diseases are different and have vastly different pathologies and etiologies.

This is why many different drugs are given to a patient to treat different ailments, targeting the specific diseases and the pathologies linked to those diseases (see again Sowers at page 1053 and pages 1054, 1st and second paragraphs). The Examiner focused on the aspect of Sowers that allegedly support the rejection while discounting the cited portions of Sowers that do not make the link as clear as the rejection spells out (see Answer at pages 8, 9

and 10). Appellants do not dispute that diabetic patients may have a higher risk of CVDs compared to healthy patients (see page 8 of the Answer referencing page 1053 of Sowers). However, page 1053 of Sowers clearly establishes that the treatment of one disease does not necessarily positively impact the other, and can even have a negative outcome on the progression of the other disease. Further, these correlations of Sowers are, at best, possible but not necessarily conclusive as the rejection makes them out to be (see page 1053, end of second col.:" may have a significant impact"," emphasis added). Indeed, Sowers on page 1054 explained that an antidiabetic treatment would not necessarily have a direct effect on cardiovascular diseases and that using an antidiabetic agent would also not be reasonably expected to treat cardiovascular diseases.

Even if the Board does not agree that the statements in Sowers cited by Appellants' are to the level of teaching that diabetes treatment does not work for treating CVDs (in the absolute), the entirety of Sowers's teachings cannot be disregarded. That is, Sowers's provides possibilities and suggests one may have a relationship to another but it cannot be ignored that Sowers's raises doubts that treatment regimens for vastly different diseases are as reasonably predictable in reality as it has been concluded on paper in the Examiner's rejection.

Appellants remind the Office that "[t]o the extent an art is unpredictable, as the chemical arts often are, KSR's focus on these "identified, predictable solutions" may present a difficult hurdle because potential solutions are less likely to be genuinely predictable." *Eisai Co. Ltd. v. Dr. Reddy's Labs., Ltd,* 533 F.3d 1353, 87 U.S.P.Q.2d 1452 (Fed. Cir. 2008).

On the basis of this Reply and the previously submitted Appeal Brief, the Examiner's rejection must be reversed as the Examiner has not satisfied the Office's initial burden to establish that the claims of this application are unpatentable under 35 U.S.C. §103(a) to a person having ordinary skill in the art in view of Liu, Sowers (*Hypertension* 2001) and Parissis (*Int J Cardio* 2002) with a reasonable expectation of success as the law requires.

Accordingly, it is respectfully requested upon consideration of the Briefs and following the oral argument (request accompanying this brief), that the Board reverse the Examiner's rejection for obviousness and send back to the examining division of the Patent Office for the issuance of a Notice of Allowance.

Respectfully submitted,

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